rejected under 35 U.S.C. §102(b) as allegedly anticipated by Thomson et al. (1998) Science 282:1145-1147 ("Thomson et al."). Claims 19-26 and 37-44 have also been rejected under 35 U.S.C. §102(e) as allegedly anticipated by Thomson, U.S. Patent No. 6,200,806 ("the '806 patent").

This response addresses each of the Examiner's rejections. Accordingly, the pending claims are in condition for allowance or at least in better condition for appeal. Favorable consideration is respectfully requested.

Turning to the rejection based on Thomson et al., it is observed that claims 19-26 and 37-44 are drawn to methods for inducing somatic differentiation of undifferentiated, pluripotent human embryonic stem cells *in vitro*, and to methods of isolating committed progenitor cells from differentiated cells. Applicants previously argued that, although Thomson et al. appear to show differentiation of cells *in vivo*, Thomson et al. do not disclose the generation of differentiated somatic lineages of non-extraembryonic type *in vitro*.

The Examiner argues that, in characterizing the cell lines, Thomson et al. use various culturing methods to differentiate the cell lines. Among the parameters taught to affect differentiation of the cell lines was the presence and absence of a feeder layer, the cell density, and various growth factors. The Examiner states that Thomson *et al.* teach that differentiation of the cells in culture results in various cell types (Figure 4B and page 12, middle of first column) and point to the references in the prior art which support more detailed methods for differentiation (page 1147; bottom of first column and in reference to citations 22-24).

In response, Applicants first respectfully submit that independent claims 19 and 37 have been canceled without prejudice. Applicants reserve the right to file a continuation application to pursue the subject matter of these canceled claims.

Applicants further submit that claims 20 and 38 have been amended to incorporate the recitations of original claims 19 and 37, respectively. As presently recited, claims 20 and 38 are directed to an *in vitro* method of inducing somatic differentiation of undifferentiated, pluripotent human embryonic stem cells by growing the stem cells under culture conditions that induce somatic differentiation. More specifically, the culture conditions comprise prolonged cultivation of the undifferentiated stem cells on a differentiation inducing fibroblast feeder layer to induce a differentiated somatic lineage or multiple differentiated somatic lineages. The conditions do not permit continued stem cell renewal but do not kill stem cells or induce their unidirectional differentiation into extraembryonic lineages.

Applicants respectfully submit that Thomson et al. do not teach methods of inducing differentiation *in vitro*. In addition, there is no recognition in Thomson et al. of the importance of fibroblast feeder layers in inducing differentiation of cells into the somatic lineages, as opposed to extraembryonic lineages. For example, the sections pointed out by the Examiner (page 1146, middle of first column), which relate to differentiation of the ES cells, show that differentiation can occur in the absence of mouse embryonic feeder layers or in the presence of fibroblasts.

Moreover, although Thomson et al. disclose culture of human ES cells and observe some differentiation of the cultured cells, the present claims are directed to methods of inducing somatic differentiation, as opposed to spontaneous differentiation including differentiation into extraembryonic lineages. It is the present invention that uniquely

recognizes the importance of specific culture conditions, in particular, the use of fibroblast feeder layers, in achieving differentiation into somatic lineages as opposed to spontaneous differentiation into extraembryonic lineages.

Accordingly, Applicants respectfully submit that the presently claimed methods are not taught by Thomson et al. Withdrawal of the rejection under §102(b) based on Thomson et al. is therefore respectfully requested.

Claims 19-26 and 37-44 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Thomson (US Patent 6,200,806, or "the '806 patent").

The Examiner admits that a unique feature of some of the cell lines disclosed by the '806 patent is their ability to differentiate into extraembryonic tissue. However, the Examiner argues that these cell lines are capable of differentiating into other cell types besides an extraembryonic lineage. The Examiner points to column 18, lines 1-43 of the '806 patent where it is described that, when cultured in high density, ES cells are capable of differentiating into multiple lineages. In addition, the Examiner points out that the '806 patent notes that, while the mechanisms controlling the differentiation of ES cells are not known, it may be possible to differentiate the ES cells to specific cell types *in vitro* (column 16; lines 45-56).

Applicants respectfully submit that the instant claims, as presently drawn, are directed to *in vitro* methods of inducing somatic differentiation of undifferentiated, pluripotent human stem cells by growing the cells on a differentiation inducing fibroblast feeder layer. Applicants submit that the '806 patent does not teach a method of inducing somatic differentiation of human ES cells by using a fibroblast feeder layer. In fact, the examples provided in the '806 patent all relate to monkey ES cells. While the reference

provides general teaching for differentiation of primate ES cells, such teaching is directed to extraembryonic differentiation (column 12, line 50 to column 13, line 52). There is no teaching anywhere of conditions that induce somatic differentiation, as opposed to extraembryonic differentiation. In column 16 line 35 to 37, the patent states: "The factors that fibroblasts produce that prevent differentiation of ES cells or feeder dependent human ES cells are unknown". In column 16, lines 51 to 56, there is a suggestion that the mechanisms for directing primate ES cells to differentiate to specific cells types is unknown and that it would be useful to elucidate these mechanisms. Clearly, there is no recognition in the '806 patent of the importance of a fibroblast feeder layer in inducing the differentiation of human stem cells into somatic lineages. A mere suggestion to identify the mechanisms and conditions that induce differentiation by no means constitutes teaching for anticipation purposes.

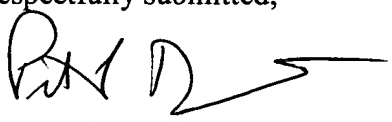
Applicants further submit that the present methods are directed to inducing somatic differentiation of undifferentiated, pluripotent human stem cells. Although the '806 patent teaches that monkey ES cells, when cultured in high density, are capable of differentiating into multiple lineages, the reference does not teach any condition that would induce differentiation specifically to non-extraembryonic lineages, i.e., to somatic lineages.

Accordingly, Applicants respectfully submit that the '806 patent does not teach the claimed invention. Withdrawal of the rejection under §102(e) based on the '806 patent is therefore respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment. The attached page is captioned "**Version with Markings to Show Changes Made.**"

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Peter I. Bernstein
Registration No. 43,497

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343
PIB/XZ:ab
Enc.: Version with Markings to Show Changes Made.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please cancel claims 19 and 37.

Please amend claims 20-26 and 38-44 as follows:

20. (Twice Amended) [A method according to claim 19] An *in vitro* method of inducing somatic differentiation of undifferentiated, pluripotent human embryonic stem cells, wherein said undifferentiated, pluripotent human embryonic stem cells are prepared by a process comprising:

obtaining an *in vitro* fertilised human embryo and growing said embryo to a blastocyst stage of development;

removing inner cells mass (ICM) cells from said embryo;

culturing said ICM cells under conditions which do not induce extraembryonic differentiation and cell death and promote proliferation of undifferentiated stem cells; and

recovering stem cells;

said method comprising growing said stem cells under culture conditions that induce somatic differentiation, wherein said culture conditions comprise prolonged cultivation of the undifferentiated stem cells on a differentiation inducing fibroblast feeder layer to induce a differentiated somatic lineage or multiple differentiated somatic lineages, said conditions do not permit continued stem cell renewal but do not kill stem cells or induce their unidirectional differentiation into extraembryonic lineages.

21. (Amended) [A] The method according to claim 20 wherein the differentiation inducing fibroblast feeder layer is a mouse and/or human fibroblast feeder layer.

22. (Twice Amended) [A] The method according to claim 20 or 21 wherein said fibroblast feeder layer comprises embryonic fibroblasts.

23. (Twice Amended) [A] The method according to claim 20 or 21 wherein the fibroblasts are tested for their ability to promote embryonic stem cell growth and to limit extraembryonic differentiation.

24. (Twice Amended) [A] The method according to [any one of claims 19,] claim 20 or 21 wherein the fibroblasts are prepared and tested for their ability to allow somatic differentiation of embryonic stem cells.

25. (Twice Amended) [A] The method according to [any one of claims 19,] claim 20 or 21 wherein said culture conditions comprise cultivating the cells for prolonged periods and/or at high density in the presence of a differentiation inducing fibroblast feeder layer to induce somatic differentiation.

26. (Twice Amended) A method for the isolation of committed progenitor cells from a culture of differentiated cells, said method comprising:

preparing a culture of differentiated cells according to [any one of claims 19,] claim 20 or 21; and

isolating committed progenitor cells from the culture.

38. (Amended) [A method according to claim 37] An *in vitro* method of inducing somatic differentiation of undifferentiated, pluripotent human embryonic stem cells, wherein said undifferentiated, pluripotent human embryonic stem cells are prepared by a process comprising:

obtaining an *in vitro* fertilised human embryo and growing the embryo to a blastocyst stage of development;

removing inner cell mass (ICM) cells from the embryo;

culturing ICM cells on a fibroblast feeder layer to obtain proliferation of undifferentiated stem cells; and

recovering the stem cells from the feeder layer;

said method comprising growing the stem cells under culture conditions that induce somatic differentiation, wherein said culture conditions comprise prolonged cultivation of the undifferentiated stem cells on a differentiation inducing fibroblast feeder layer to induce a differentiated somatic lineage or multiple differentiated somatic lineages, said conditions do not permit continued stem cell renewal but do not kill stem cells or induce their unidirectional differentiation into extraembryonic lineages.

39. (Amended) [A] The method according to claim 38 wherein said differentiation inducing fibroblast feeder layer is at least one of a mouse fibroblast feeder layer or human fibroblast feeder layer.

40. (Amended) [A] The method according to claim 38 or 39 wherein said fibroblast feeder layer comprises embryonic fibroblasts.

41. (Amended) [A] The method according to claim 38 or 39 wherein the fibroblasts are tested for their ability to promote embryonic stem cell growth and to limit extraembryonic differentiation.

42. (Amended) [A] The method according to [any one of claims 37,] claim 38 or 39 wherein the embryonic fibroblasts are prepared and tested for their ability to allow somatic differentiation of embryonic stem cells.

43. (Amended) [A] The method according to [any one of claims 37,] claim 38 or 39 wherein said culture conditions comprise cultivating the cells for prolonged periods and/or at high density in the presence of a differentiation inducing fibroblast feeder layer to induce somatic differentiation.

44. (Amended) A method for the isolation of committed progenitor cells from a culture of differentiated cells, said method comprising:

preparing a culture of differentiated cells according to [any one of claims 37,] claim 38 or 39; and

isolating committed progenitor cells from the culture.